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Original Research Article

Personalized Pain Goals and Responses in Advanced Cancer Patients

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Abstract

Objective. To assess the personalized pain intensity goal (PPIG), the achievement of a personalized pain goal response (PPGR), and patients' global impression (PGI) in advanced cancer patients after a comprehensive pain and symptom management. **Design**. Prospective, longitudinal **Setting**. Acute pain relief and palliative/supportive care. **Subjects**. 689 advanced cancer patients. **Methods**. Measurement of Edmonton Symptom Assessment Score (ESAS) and personalized pain intensity goal (PPIG) at admission (T0). After a week (T7) personalized pain goal response (PPGR) and patients' global impression (PGI) were evaluated. **Results**. The mean PPIG was 1.33 (SD 1.59). A mean decrease in pain intensity of − 2.09 was required on PPIG to perceive a minimal clinically important difference (MCID). A better improvement corresponded to a mean change of − 3.41 points, while a much better improvement corresponded to a mean of − 4.59 points. Patients perceived a MCID (little worse) with a mean increase in pain intensity of 0.25, and a worse with a mean increase of 2.33 points. Higher pain intensity at T0 and lower pain intensity at T7 were independently related to PGI. 207 (30.0%) patients achieved PPGR. PPGR was associated with higher PPIG at T0 and T7, and inversely associated to pain intensity at T0 and T7, and Karnofsky level. Patients with high pain intensity at T0 achieved a favorable PGI, even when PPIG was not achieved by PPGR. **Conclusion**. PPIG, PPGR and PGI seem to be relevant for evaluating the effects of a comprehensive management of pain, assisting decision-making process according to patients' expectations. Some factors may be implicated in determining the individual target and the clinical response.

Key Words: Cancer Pain; Clinical Response; Pain Intensity

Introduction

Patients with cancer often experience pain [1]. The prevalence of pain in this population has been estimated to be >75% for those with advanced disease [2]. Cancer pain is a complex multidimensional phenomenon. Inadequate pain assessment is one the most relevant barriers to providing appropriate pain management. Thus, patient-reported pain and symptom evaluation has been considered the gold standard to assess clinical response. The Edmonton Symptom Assessment System (ESAS) is one of the most common tools used to evaluate both physical and psychological symptoms. This simple instrument, which is easy to use and repeatable, is based on a unidimensional numeric rating scale ranging from 0 (no symptom) to 10 (worse possible) for each symptom taken into consideration [3]. However, this instrument may have some limitations because patients may individually

interpret the scale, variably expressing intensity. On the other hand, the clinical response after initiating a particular treatment is difficult to assess, as the minimal clinically important difference (MCID) is often not established. The MCID is considered the smallest amount of change required to impact a patient's feeling of improvement or deterioration after treatment. The MCID has been the subject of recent research. Some tools have been reported as methods to assess MCID, including the distribution method [4–6] and the use of anchors, such as the change of intensity categories of well-being [7], the optimal balance between sensitivity and specificity, and the magnitude of change in outcome reported by the patient. The need to evaluate the individual variations in assessing scales or numbers remains of paramount importance. Thus, the use of the Patient Global Impression (PGI) scale has been suggested. This is a validated global rating-of-change scale to assess patients' subjective response, as it is based on the individual feeling of improvement or deterioration after receiving a drug [8]. Furthermore, a personalized symptom goal has been recently introduced to tailor pain (Patients' Pain Intensity Goal [PPIG]) and symptom management, providing a simple and individualized "target" score on the ESAS [9,10]. Therapeutic attempts should try to reach such a threshold for an intrapatient determination of an expected response to any treatment. The concept of Personalized Pain Goal Response (PPGR), which is both practical and meaningful, represents the achievement of the expected PPIG, individually determined. Factors associated with PPIG and PGI have never been examined. Studies have assessed these points, even for pain [7,9–12]. However, data were retrospectively examined or performed in an outpatient setting, with variable intervals for the follow-up. An optimal characterization of PPIG and a study of factors associated with PPGR and PGI, as perceived by patients, would help clinicians to maximally personalize pain management and to evaluate meaningful changes. This is even more important in a palliative care unit, the setting where pain and symptom management can be more rapid and effective because daily assessment, expertise, and timely therapeutic changes may provide better control of pain and symptoms in a short period.

This study was performed to characterize the PPIG, PPGR, and PGI after comprehensive pain management in advanced cancer patients. The secondary aim was to assess the factors that can influence these outcomes.

Methods

This is a subanalysis of a large international study of advanced cancer patients performed at admission to five palliative care units in Italy, Brazil, and Greece [13]. The ethical committees at all participating centers approved the study. All participants provided written informed consent. Participating centers were tertiary care palliative care units within a comprehensive cancer department.

Participants

A comprehensive pain and symptom assessment was performed by a specialist palliative care physician. Inclusion criteria were age ≥18 years and a diagnosis of advanced cancer. Exclusion criteria were no pain, a short life expectancy (less than two weeks), cognitive failure (a score of ≥13 on the Memorial Delirium Assessment Scale [MDAS]) [14].

Data Collection

Patients' characteristics, including age, gender, education level, and cancer diagnosis, were recorded, as well as initial Karnofsky performance status.

Symptom intensities included in the ESAS (pain, shortness of breath, fatigue, nausea, depression, anxiety, drowsiness, insomnia, appetite, feelings of well-being) were measured at admission (T0). The same measurements were performed seven days after starting a comprehensive palliative care treatment (T7). The comprehensive palliative care intervention was based on specialized assessment and treatment of symptoms. No strict protocols were given, and treatments were based on local policy. Researchers participating in the study were experienced in providing palliative care. One week was assumed to be an acceptable time to experience the effects of a clinical intervention.

The ESAS is a self-reported tool assessing the intensity of most common psychological and physical symptoms; it uses a numeric rating scale ranging from 0 (no symptom) to 10 (worst intensity) points to examine symptom intensity over the past 24 hours. It is a valid and reliable tool for assessing the overall symptom burden and is sensitive to changes produced by treatment [3]. A screening tool for history of alcohol dependence (CAGE: cut down, annoy, guilt, eye-opener) was also used, as a positive CAGE score (2) has been variably shown to have prognostic value in opioid management [15].

At T0, patients were asked about their PPIG. The question was: "At what level would you feel comfortable with pain?" using the numeric rating scale used for ESAS [12]. One week (T7) after starting comprehensive pain and symptom management tailored to patients' needs and local policy, ESAS and PPIG were measured to evaluate the changes. Patients achieved the PPGR if their intensity measured at T7 was equal to or less than their expected PPIG. At the same interval (T7), PGI (improvement or deterioration) was measured on a scale from +3 to −3 (much better, better, a bit better, the same, a little worse, worse, and much worse, respectively). PGI has been used assess a clinically significant changes in pain intensity [12,13]. The MCID was calculated by PGI at T7 (a bit better or a little worse, respectively).

Statistical Analysis

Quantitative and qualitative data, including descriptive statistics, were analyzed for all items. Continuous data

Table 1. Characteristics of patients

Age, mean (SD) [range], y		64.3 (12.5) [18–97]
Gender (M/F), No. (%)		1,558 (56.2)/1,213 (43.8)
Karnofsky mean (SD) [range]		60.3 (19.6) [10–100]
Primary tumor, No. (%)	Lung	756 (27.3)
	Gastrointestinal	478 (17.2)
	Breast	280 (10.1)
	Pancreas	271 (9.8)
	Urological	175 (6.3)
	Prostate	138 (5.0)
	Head-neck	141 (5.1)
	Gynecologic	126 (4.5)
	Liver	94 (3.4)
	Hematological	62 (2.2)
	Sarcoma	46 (1.7)
	Others	308 (11.1)
Disease, No. (%)	Loco-regional	499 (18.0)
	Metastatic	2,272 (82.0)
Anticancer treatment, No. (%)	Disease-oriented	2,067 (74.6)
	Palliative Care	585 (21.1)
Place of visit, No. (%)	Outpatients	761 (27.5)
	Day hospital	297 (10.7)
	Home care	502 (18.1)
	Hospice	89 (3.2)
	Hospital inpatient	1,122 (40.5)
Setting, No. (%)	Palliative care	623 (22.5)
	Oncology	1,397 (50.4)
	Pain therapy	738 (26.6)
	Radiotherapy	13 (0.5)
Mean background pain intensity at T0 (SD)		2.9 (1.8)
Mean opioid doses (SD), mg/d		81.3 (95.7)

were expressed as mean ±SD, unless otherwise specified. Pearson's chi-square test and the Fisher exact test, as needed, were used for frequency analysis. To compare mean patient characteristic changes and their corresponding SDs, with 95% confidence intervals, the paired-samples Student *t* test was used, with I type error set at 5%. PGI was categorized into three classes: deterioration (PGI ≤ -1), no change (PGI = 0), and improvement (PGI ≥ 1). The level of pain intensity was categorized into three classes (mild = 1–3, moderate = 4–6, severe = 7–10). Univariate analysis of variance (ANOVA) was performed to evaluate difference between patients' clinical characteristics, and post hoc analysis with the Bonferroni test was used to determine whether there were pairwise differences. Multivariate logistic regression analysis was performed on the significant variables using ANOVA to evaluate the correlation between patient characteristics (independent variables) and PGI groups (dependent variables). Pearson correlation analysis was conducted to assess the association between PPGR and patient clinical variables. Data were analyzed by IBM SPSS software, version 22 (IBM Corp., Armonk, NY, USA). All *P* values were two-sided, and $P < 0.05$ was considered statistically significant.

Results

From the original study, 689 patients with pain at T0 and complete assessment at T7 were analyzed. The characteristics of these patients are reported in Table 1. The mean age (SD) was 66.7 (11.8) years, 354 patients (51.4%) were males, and 396 patients (57.5%) had a Karnofsky level of ≤50. The mean Karnofsky level (SD) was 53.7 (12.9). The mean MDAS value (SD) was 4.2 (3.4). One hundred sixty-four patients (23.8%) had an MDAS in the range of 7–12 at T0. Twenty-six patients (3.8%) were CAGE positive.

The mean pain intensity (SD) was 5.98 (2.4) at T0 and 3.36 (2.2) at T7. The mean difference (SD) was 2.62 (2.2) points, which was statistically significant ($P < 0.0005$). At T0, 44.3% of patients reported severe pain intensity (≥7/10), whereas only 8.1% of patients reported severe intensity at T7 ($P < 0.0001$, chi-square test).

PPIG

The majority of patients (87.5%) indicated a PPIG of ≤3 as a target. The mean PPIGs at T0 and T7 (SD) were 1.33 (1.59), and 0.91 (1.23), respectively (Δ–0.42 [1.36]). The difference was statistically significant (<0.0005). Eighty-three patients (12%) had a PPIG of ≥5. A higher PPIG (>4) was significantly associated with a lower Karnofsky level (odds ratio [OR] = 0.97, 95% confidence interval [CI] = 0.95–0.98, $P = 0.002$) and higher pain intensity at T0 (OR = 1.61, 95% CI = 1.41–1.83, $P < 0.0005$).

PGI

Five hundred thirty-four patients (77.5% reported an improvement in PGI [at least bit better]) (Table 2). Patients perceived an MCID (a bit better) with a mean decrease in pain intensity of –2.09. A better improvement corresponded to a mean change of –3.41, whereas a much better improvement corresponded to a mean change of –4.59 points on the pain intensity scale. In 143 patients (20.7%), no changes (no improvement, no deterioration) were recorded. In a low number of patients, pain intensity worsened. Patients perceived an MCID (a little worse) with a mean increase in pain intensity of 0.25. They perceived a worse with a mean increase of 2.33 points.

In the univariate analysis, pain intensity at T0, MDAS, and PPIG at T0 were related to PGI, categorized into three classes (no change, improvement, deterioration) (Table 3). Pain intensity at T7 was inversely correlated with PGI (the lower the pain intensity, the higher the PGI). In the multiple logistic regression analysis, higher pain intensity at T0 and lower pain intensity at T7 were independently related to PGI (Table 4).

PPGR

At T7, 207 (30.0%) patients achieved their target (PPIG). PPGR was correlated with PPIG both at T0 and T7 and

Table 2. Minimal clinical difference according to Patient Global Impression after comprehensive pain management

		PGI						
ESAS Change Score		Much Better	Better	A Bit Better	The Same	A Little Worse	Worse	Much Worse
Pain	No.	147	162	225	143	8	3	1
	Mean (SD)	–4.59 (2.01)	–3.41 (1.86)	–2.09 (1.33)	–0.84 (1.84)	0.25 (1.75)	2.33 (0.58)	0.0

ESAS = Edmonton Symptom Assessment System; PGI = Patient's Global Impression.

Table 3. ANOVA analysis

		PGI			
		No Change	Improvement	Deterioration	*P*
Variables	No.	143	534	12	
Age, y	Mean (SD)	67.3 (12.1)	66.5 (11.9)	68.2 (7.4)	0.693
Karnofsky	Mean (SD)	55.6 (12.9)	53.2 (12.9)	54.2 (13.1)	0.137
Pain T0	Mean (SD)	4.6 (2.7)	6.4 (2.1)	4.3 (2.1)	<0.0005
					1 vs 0
					1 vs 2
Pain T7	Mean (SD)	3.8 (2.9)	3.2 (1.9)	5.1 (1.9)	0.001
					1 vs 0
					1 vs 2
MDAS	Mean (SD)	3.8 (3.2)	4.4 (3.4)	2.1 (2.6)	0.007
					1 vs 2
Patient goal T0	Mean (SD)	0.7 (1.2)	1.5 (1.7)	0.8 (1.1)	<0.0005
					1 vs 0
Patient goal T7	Mean (SD)	0.7 (1.1)	0.9 (1.3)	1.0 (1.2)	0.061

Patient Global Impression was categorized into three classes: no change (PGI = 0), improvement (PGI ≥1), deterioration (PGI ≤1).
ANOVA = analysis of variance; MDAS = Memorial Delirium Assessment Scale; PGI = Patient Global Impression.

Table 4. Patient Global Impression

PGI		OR	95% CI	*P*
No change	PAIN T0	2.177	1.310–3.619	0.003
	PAIN T7	0.437	0.270–0.706	0.001
	MDAS	1.227	0.955–1.577	0.109
	Patient pain goal T0	0.925	0.536–1.595	0.778
Improvement	PAIN T0	4.736	2.800–8.011	<0.0005
	PAIN T7	0.217	0.132–0.356	<0.0005
	MDAS	1.260	0.978–1.622	0.074
	Patient pain goal T0	1.259	0.728–2.178	0.409

Multiple logistic regression in reference to PGI category of deterioration.
CI = confidence interval; MDAS = Memorial Delirium Assessment Scale; OR = odds ratio; PGI = Patient Global Impression.

was inversely correlated to pain intensity recorded at T0 and T7 and a lower Karnofsky level (Table 5).

Patients with higher pain intensity at T0 had a favorable PGI ($P < 0.0001$), even when the target, based on PPIG response, was not achieved. No significant differences among categories of pain intensity were found for PPGR ($P > 0.05$) (Table 6).

Discussion

This subanalysis of data gathered in an international multicenter study, which recruited a large number of patients, provided interesting information to help physicians in personalizing pain management and realizing how much patients would like to improve their pain and how effectively physicians can help them achieve their target. Pain intensity significantly decreased after comprehensive palliative care treatment.

PPIG

Most patients indicated a PPIG of ≤3, confirming existing data from previous studies [16]. Although in these studies PPIG remained unchanged at undetermined follow-up visits [9,16,17], in the present study, PPIG decreased after one week, as if patients wanted to raise their expectations once they had an improvement in pain intensity or after achieving their initial target. The long follow-up period of these studies and the short and acute period of the present study could explain the differences.

PGI

In most patients PGI for pain was positive, given that 534 patients reported an improvement in pain intensity after one week of treatment. One week is considered to be a meaningful time frame to stabilize patients admitted to a place like a palliative care unit, where efforts to manage symptoms are intensive and effective [18]. Patients perceived an MCID with a decrease in pain intensity of about 2 points. For perceiving a better improvement, patients required a decrease in pain intensity of about 3.5. A much better improvement was perceived with a mean decrease of 4.5 points. In previous studies, a lower

Table 5. Factors correlated with Patient Pain Goal Response

		Patient Pain Goal Response
Age	Pearson correlation	0.028
	P (2-tailed)	0.460
	No.	686
Gender	Pearson correlation	–0.024
	P (2-tailed)	0.527
	No.	686
Karnofsky	Pearson correlation	–0.151**
	P (2-tailed)	<0.0005
	No.	683
Pain T0	Pearson correlation	–0.272**
	P (2-tailed)	<0.0005
	No.	686
Patient pain goal T0	Pearson correlation	0.508**
	P (2-tailed)	<0.0005
	No.	686
Pain T7	Pearson correlation	–0.778**
	P (2-tailed)	<0.0005
	No.	686
Patient pain goal T7	Pearson correlation	0.115**
	P (2-tailed)	0.003
	No.	686

Table 6. Patient Pain Goal Response and Patient Global Impression, according to the categories of pain intensity measured at T0

	Mild, No. (%)	Moderate, No. (%)	Severe, No. (%)	Total
Pain T0	127	257	305	689
PPGR (≥1)	42 (33.1)	77 (30.0)	85 (27.9)	204
PGI (≥1)	53 (41.7)	215 (83.6)*	266 (87.2)*	534

PGI = Patient Global Impression; PPGR = Patient Pain Goal Response.
*$P < 0.0001$ in respect to mild pain intensity.

MCID was found [7,12]. The retrospective nature of design, the longer and not constant intervals among observations, the use of different categories anchored to the well-being scale [11], or the setting (radiotherapy, outpatients), may explain the differences. Some studies have reported more relevant changes of pain intensity to perceive a meaningful clinical benefit, including a 33% decrease or a reduction of two or more points [19,20], confirming data found in this study.

The factors principally related to improvement in PGI have never been assessed. In this study, the higher the pain intensity, the better the PGI, although not all patients were able to achieve their target. It is likely that a more evident feeling of improvement perceived by patients when they perceive a net decrease in pain intensity (about halving the pain intensity with about 2.5 points of difference) explains this finding. Similarly, higher PPIG was also independently associated with a positive PGI, possibly because the level expectation is easier to be reached with just a little change in pain intensity. Thus, patients who accept a higher level of pain intensity are more likely to achieve better satisfaction. Eighty-three patients (12%) had higher values of PPIG at admission. These patients are likely to require only minimal changes in pain intensity for a positive PGI. On the other hand, a low level of pain intensity at T7 was associated with a better PGI, as a consequence of adequate pain management.

In some studies, initial pain intensity has been found to be a negative factor for pain prognosis [16,21–23]. These studies, however, clearly showed that clinical undertreatment was responsible for the outcome. In fact, patients were stabilized for a very long time (one to three weeks), suggesting a nonoptimized method for opioid dose titration. In other circumstances, a retrospective long follow-up in outpatients (three weeks), based on only one therapeutic intervention, would have biased the outcome. Indeed, pain intensity is a dynamic concept, depending on the moment in which the patient is intercepted [18]. Several surveys and also daily practice suggest that pain control is commonly achieved in a few days in the majority of patients by using personalized opioid dose titration [24–30]. Data from this study confirm that the higher the level of initial pain intensity, the better the patient satisfaction score after proper pain management.

PPGR

Thirty percent of patients achieved their target (PPIG) after proper pain management. This percentage was lower than that of patients with a positive PGI. In patients with higher pain intensity or a lower Karnofsky level, PPGR was more likely to be achieved, allowing the patient to reach the level of PPIG expected. Thus, a higher PPIG allowed the achievement of a better PPGR, as small improvements were sufficient to obtain the target level desired by patients. This finding reflects the features of PGI. Patients with higher pain intensity may have lower expectations when rating their PPGI scores as high, which means that active pain management may have a greater opportunity to achieve PPGR. Patients with a lower Karnofsky status may have a more positive impression after palliative care treatment or may merely have lower expectations. This observation deserves further study.

This study has some limitations. In comparison with previous trials examining issues regarding clinical changes as perceived by patients and PPIG, data were obtained from patients recruited in palliative care units, where it is likely that symptom assessment and treatments are more intensive. Thus, these data are not generalizable to outpatients or home care settings. A PPIG scale was used to test MCID in this study. That is the way patients may individually perceive clinical change. This tool proved to be repeatable and easy to understand, even though it lacks other external criteria.

Conclusions

The PPIG allows clinicians to individualize patient care and ensures intrapatient determination of a practical and meaningful pain response. The PPIG, PGI, and PPGR are measurements that are relevant to the assessment and decision-making process, according to patients' expectations. Some factors, such as pain intensity, PPIG, and Karnofsky, may influence clinical response, assessed by PGI and PPGR. Further studies should investigate these aspects in other palliative care settings.

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